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A Sequential Developmental Field Defect of the Vertebrae, Ribs, and Sternum, in a Young Woman of the 12th Century AD

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ABSTRACT Changes in the vertebral column are often noted in skeletal material. Descriptions of these anomalies are often lacking, and their developmental origins are not often discussed. The skeleton of a young woman from the medieval cemetery of Tirup, in Denmark, has multiple defects of the axial skeleton, including extra thoracic and lumbar vertebrae, border shifting, extra ribs, block vertebra, and deformed sternum. This case study is particularly interesting because of the number and diversity of anomalies seen; the rarity of these defects, even in living populations; and her survival to adult age. Careful analysis of the bones and use of the morphogenetic method of determining development stages has led to the conclusion that the initial defect probably occurred very early in development, during blastogenesis, with the initial development of at least two extra somitomeres in the paraxial mesoderm. These extra elements in turn led to problems in union and differentiation, and later chondrification and ossification of the vertebra. The malformations of the vertebrae also induced changes in the ribs and sternum. The initial error of segmentation is identified as a developmental field defect, and the cascade of anomalies seen is a developmental sequence caused by the initial field defect. The genetic and environmental causes of developmental field defects are reviewed. Am J Phys Anthropol 111:355–367, 2000.

Developmental defects in skeletal material show the plasticity of the human skeleton, give insight into the stages of development of the human form, and allow us to make inferences about the lives of individuals who lived in the past. Because the causes of these defects are often a combination of environment and genetics, even one individual can lead our forming to interesting conclusions. Putting an individual within the framework of a local population can give clues about the genetic and social structure of that society as well.

In this paper, the skeleton of a young medieval woman is described. Although studies in the archaeological and anthropological literature often mention slight developmental defects of the axial skeletal (i.e., Chase, 1997; Dickel and Doran, 1989; Kaufman, 1974), this case is especially interesting due to the number and diversity of vertebral and other skeletal abnormalities. Other reports describing two extra vertebral elements have included lumbarized sacral vertebrae (see Barclay-Smith, 1911); there are no other reports describing two extra presacral verte-

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bral elements or investigating the developmental sequence leading to these changes. The morphogenetic approach to understanding development defects of the axial skeleton uses careful examination of the process of human embryonic development to determine when and how vertebral defects are initiated (Barnes, 1992).

BACKGROUND

Tirup

The Early Medieval cemetery site of Tirup in Denmark was completely excavated in the 1980s by Danish archaeologists, who discovered 619 graves within the bounds of a walled cemetery (Boldsen, 1996; Kieffer-Olsen et al., 1997). Tirup is located near the east coast of the Jutland peninsula in Denmark, 5 km west of Horsens. The site lies on a hill between two major drainages, and the soil is sandy and well-drained, well-suited for farming. Fifty percent of the excavated remains were those of children (under 18 years). One hundred to 120 were identified as adult females, and 120–140 could be identified as adult males. The remainder were adults of unknown sex. Approximately 100 graves were empty, as a result of either disinterment (fewer than ten) or lack of bone preservation. The empty graves included both adult and children's graves, judging from the latter's size. The cemetery was first used ca. 1130 AD, with the supporting town averaging between 70 and 80 individuals at any time, although this number fluctuated through its occupation. This number of people could have comprised about ten households, depending on their size and composition. The town and cemetery were abandoned between 1320 and 1340 (before the Black Death in 1348) during the Late Medieval Agrarian Crisis, perhaps because the population dropped below a critical level needed for efficient open-field farming. The last few individuals to be buried were disinterred at this period and removed (Boldsen et al., 1985).

Developmental field theory

Congenital defects offer a window into patterns of development. By studying patterns of defects found in fetuses and live-born children, the sequence of development events have been determined. The earliest period of development of the embryo, from fertilization to days 27–28, is called blastogenesis, and is the period of pattern formation in the embryo (Martinez-Frias et al., 1998). Later development in utero is divided into two periods (Opitz, 1993): organogenesis, from the end of blastogenesis until the end of the eighth week; and phenogenesis, from the end of organogenesis until birth. During organogenesis, the organs are formed and their cells differentiate into their final role. Phenogenesis is the period of growth (Opitz, 1993). Segmentation, including early vertebral formation, happens during blastogenesis (Martinez-Frias and Frias, 1997b).

In the earliest stages of development, similar defects are created by many different causes (Opitz, 1993). It is theorized that during blastogenesis and organogenesis, the tissues are subdividing from generalized tissue into components that will later form the adult structure (Martinez-Frias et al., 1998). During this phase, disruptions of any type in the same tissues can cause patterning of defects. These groups of tissue have been termed *developmental fields*, and are defined by Opitz (1993:10) as "any morphologically reactive unit of the developing organism that leads to final structure." Defects that occur from disruptions of the fields are called *developmental field defects* (Martinez-Frias et al., 1998). Developmental field defects that occur during blastogenesis are termed *blastogenetic field defects*, and are generally more severe and complex than those that occur during organogenesis (Opitz, 1993).

Segmentation defects of vertebrae are blastogenetic developmental field defects (Martinez-Frias and Urioste, 1994), which often have more than one manifestation in the fetus (Martinez-Frias et al., 1998). They are classified as *sequences*, *associations*, and *syndromes*. A sequence "is characterized by effects evidently secondary to a primary anomaly as a cascade of consequences with known pathogenetic mechanisms" (Martinez-Frias et al., 1998: 293). Thus, sequences arise from a single blastogenetic defect. Associations are multiple developmental field defects that arise because the embryo is

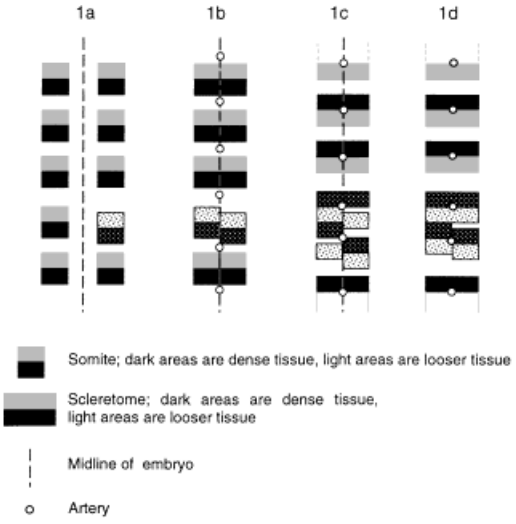

Fig. 1. Development of normal and defective vertebrae. Vertebrae involved in malformation are stippled. See text for details.

disrupted in a way that causes several different fields to develop abnormally (Martinez-Frias, 1994). Syndromes are descriptions of sets of defects, which may be sequential or associative, and should have no implication about the developmental origin (Martinez-Frias et al., 1998).

Normal vertebral, rib, and sternal development

The organization and design of mature vertebrae and ribs are laid down very early in development during blastogenesis (Opitz, 1993), as described by Collins (1995), Barnes (1991), and Jacobson (1998). By the days 5–6 post-conception, the embryo is becoming organized linearly. Somitomeres, groups of mesoderm tissue that begin the segmentation plan, form along the midline in an anterior to posterior direction. Normally, about 51 sets of somitomeres form, with the superior seven later becoming incorporated into the basal portion of the skull, and the inferior 44 later developing into vertebrae. Between the day 20 and 22, the mesenchyme organizes along these somitomeres to form undifferentiated blocks of cells, the somites, on either side of the midline of the developing embryo (Fig. 1a). An equal number of these somites develop independently on either side, making 44 pairs, with the superior four later forming portions of the occipital bone, the next eight laying the foundation for the cervical vertebrae, 12 later becoming thoracic vertebrae, five later forming lumbar vertebrae, five establishing sacral elements, and the remaining later forming the coccyx (Collins, 1995). Within the next few days, these blocks undergo a number of changes. They line up, starting with the cervical area, across the midline. Portions of these then break away to form one block, called a sclerotome, that encircles the primitive notochord (Fig. 1b). At the same time, the cells within the sclerotome start rearranging themselves, with the inferior half becoming more dense and organized. The beginning of the arteries that will supply the forming vertebrae develop between the sclerotomes. These dense areas then begin to change, separating from the looser superior part of the sclerotome (Fig. 1c), and falling to join the less dense superior half of the sclerotome below (inferior), surrounding the artery. This new, reversed block of tissue is the basis of the vertebra (Fig. 1d). During the re-fusion of the sclerotome, the dense tissue is also moving posteriorly, leaving the less dense tissue to form most of the vertebral centrum. The cells from the dense region migrate around the neural tube (the precursor to the spinal cord) to lay down the basis for the neural arches of the vertebrae and the ribs (Barnes, 1992; Collins, 1995; Jacobson, 1998).

The chondrification and ossification occur during organogenesis and phenogenesis (Opitz, 1993), and are further described by Collins (1995), and Barnes (1991). After the sclerotomes have formed the foundation for the vertebrae and ribs, four to six chondrification sites in each vertebra appear around 6–7 weeks post-conception. Four of these form cartilage in the vertebra, with two centers in the body (which quickly unite to form a single centrum chondrification site) and one in each half of the arch. In the thoracic region, an addition two chondrification sites appear on either side for the ribs. Starting in the eighth week, ossification centers appear; one in the centrum and two in the arches at the pars interarticularis. The centers ossify the cartilage starting in

the cervicothoracic region, then in the thoracolumbar region. There are typically three separate bony sections to the vertebra at birth — the lateral halves of the arches, and the centrum. The arches fuse to each other in the first year after birth (Collins, 1995), and the arches fuse to the centrums around 3–6 years after birth (Collins, 1995; Krogman and Iscan, 1986). Ribs begin to ossify in the ninth week, starting around the sixth and seventh ribs (Barnes, 1992; Collins, 1995).

Ribs form from the costal processes of the thoracic vertebrae by the fourth week. They begin to chondrify in the sixth to seventh week, then are ossified in the eighth week. The developing ribs elongate from the vertebra, and move around the torso. The first through seventh meet the sternal plates (Collins, 1995).

The sternum develops from a different origin. It begins as mesenchymal tissue that organizes itself into sternal plates on either side of the midline in the sixth week after conception. These almost immediately chondrify, and are pushed by the developing ribs toward the center to unite, which occurs around week nine. After they join, the ribs influence the tissue to segment into four sections. Around the fifth fetal month, each segment ossifies from one or two centers (Barnes, 1992; Collins, 1995).

Genetic and environmental influences on development

There are a complex of environmental and genetic mechanisms that combine to regulate the development of the vertebral column, as described in Collins (1995), Weiss (1993), and Hunt (1998). In vertebrae, it is suspected that a set of regulatory genes are involved in the differentiation of the somites. These genes, called *homeobox genes*, produce proteins that bind to specific DNA regions, causing expression of genes on that chromosome. One set of these genes, found in invertebrate and vertebrate animals, is called Hox (in humans, it is designated HOX). Experiments show that Hox genes are involved in the regulation of segments along a linear axis in an embryo. There are four clusters in humans, found on chromosomes 2, 7, 12, and 17. They are found linearly along the DNA, and the closer a Hox gene is to the 3′ end of the DNA, the more superior the expression will be (Collins, 1995). It appears that the combination of these proteins that together "tell" a somite its future identity, and the addition or deletion of the normal sets of homeobox proteins during critical times in development can induce a shift, causing one vertebra to look like another (Weiss, 1993). Researchers have shown that the absence of the homeobox gene product Hoxc-4 in mice produces shifting in the cervical and thoracic vertebra (Saegusa et al., 1996). These can also cause a change in the number of digits in humans, although it has not been shown for vertebrae specifically (Innis, 1997).

Cells are not able to spontaneously activate regulatory genes, such as Hox. A signal, called a *morphogen* or a *Hox gene enhancer* or *promoter*, is needed from outside. This morphogen diffuses in the region of cells that have morphogen receptors. When a morphogen binds to a receptor, it activates regulatory genes, like Hox, within the cell. How morphogens act, their identities, and origin remains a debate (Hunt, 1998). It is known, however, that environmental substances, such as retinoic acid, can act as morphogens (Lufkin, 1997). The morphogen, morphogen reception, regulatory gene complex is subject to many disruptions. Environment or uncontrolled internal production of morphogens have the potential to induce regulatory genes where they would normally not be expressed. Morphogen receptors that are missing or malformed may not be able to receive messages sent to differentiating cells. And mutations in the regulatory gene complex with a cell or cells could make the cell unable to respond correctly to a morphogen message.

Developmental field defects of the vertebrae can be caused by genetic or environmental factors. Presumably, genetic causes of defects act by producing a malfunctioning product or not producing one at all, disrupting the chain of events. Environmental agents cause defects by introducing chemicals that disrupt this pathway, or by physically disabling the process.

There are multiple ways that genetic anomalies can cause defects. In a study of

110 infants with major blastogenetic segmentation anomalies of the vertebrae and ribs (identified with a systematic physical examination within a few days of birth), 13 (11.8%) were know to be of genetic origin, either single gene disorders or chromosomal aberrations (Martinez-Frias and Urioste, 1994). Additional evidence for the genetic nature of some of these defects comes from family studies of babies with developmental field defects. In several studies, the mothers of 20,891 Spanish infants born with defects were interviewed about previous pregnancies and family structure. Mothers of infants with blastogenetic defects (including vertebral segmentation defects) had significantly more spontaneous abortions in previous pregnancies than those of children with milder defects. The latter group of mothers, in turn, had more miscarriages than those of the control group of children with no defects (Martinez-Frias and Frias, 1997a). In another study of the same group of infants, it was found that children with blastogenetic defects were much more likely to come from consanguineous parents than children with milder defects, and the controls were even less likely to come from closely related parents. Additionally, all children with defects were much more likely to have first degree relatives with developmental defects (Martinez-Frias and Frias, 1997b). However, it is worth noting that cases suggesting a genetic basis for defects constitute only a small percentage ($<$10%) of all children with defects (Martinez-Frias and Frias, 1997a,b).

It has been shown that the diet of the mother and the availability of specific nutrients (zinc, in particular) is also very important (Barnes, 1992; Zimmerman and Lozzio, 1989). Additionally, Opitz (1993) lists chemical (e.g., thalidomide, cocaine, cortisone), infectious (e.g., rubella, toxoplasmosis, syphilis), and physical (e.g., rupture of chorion, fetal graft-versus-host disease, and twinning disruptions) factors that can cause developmental field defects. Also, children of diabetic mothers have higher rates of all types of developmental defects, presumably due to an unusually high level of a maternal hemoglobin variant or genetic predisposition (Opitz, 1993). In the study of 110 infants with major defects of the vertebrae and ribs, 13 cases (11.8%) were from mothers with diabetes, constituting all cases of known environmental cause (Martinez-Frias and Urioste, 1994).

The majority of cases of blastogenetic field defects have no identifiable cause. In the study of 110 infants with major defects of the vertebrae and ribs, 84 (76.4%) had unknown causes (Martinez-Frias and Urioste, 1994). Ninety percent of the infants with blastogenetic field defects had no first-degree relative with defects (Martinez-Frias and Frias, 1997b). It may be that parental recall of environmental factors 9 months previous is poor. Also, the pathways leading to segmentation and differentiation are so complex that it is impossible, at this point, to identify all the genes involved. Therefore, finding specific mutations in individual cases is unlikely.

Archaeological examples of vertebral abnormalities

Cases of vertebral abnormalities have been published in archaeology and anatomical literature. These usually include spina bifidas (Dickel and Doran, 1989) or listings of abnormalities (Kaufman, 1974; Chase, 1999). However, a single case of an Egyptian woman was described by Barclay-Smith (1911) that shows similarities to the form of the woman from Tirup. The Egyptian skeleton was incomplete, consisting only of the skull, vertebrae, and several ribs. In this case, there were eight cervical vertebrae with the normal number of the remaining vertebrae. However, cervical vertebrae show blocking, and there are transitional vertebrae at the cervicothoracic, thoracolumbar, and lumbosacral borders. This vertebral column also exhibits scoliosis, which is not seen in the skeleton investigated here. It appears that this is also a prehistoric case of a sequential developmental defect.

CASE STUDY OF GRAVE 82

The skeleton investigated in this paper is Grave 82 (G82), from the Tirup cemetery site. The skeleton is well preserved and nearly complete. The burial probably dates to the latter half of the cemetery use, as indicated by its body and hand position in the grave (Kieffer-Olsen, 1993). It was deter-

mined to be the remains of woman, using separate assessment of the pelvis and skull. This was independently verified by both authors and an another osteologist (J. L. Boldsen). The woman was between 20 and 24 years at death. This age determination was made by a combination of standard morphological aging techniques and the newly developed transition analysis method using skull sutures, iliac auricular surfaces, and pubic symphyses (Milner et al., 1997). Many of the epiphyseal lines are still visible on the long bones, indicating a younger adult. The third molars were erupted.

Although many individuals in the modern literature with these types of defects have unusually short stature and are sometimes classified as dwarfs (i.e., Anhalt et al., 1995), this individual was shorter than average for this population, although she was not statistically different than expected. Two different measures of height support this. Her length in the grave (a measurement taken by the excavators from the superior portion of the skull to the inferior portion of the calcaneus) was measured at 149 cm, while average in the cemetery for adult females was 155, putting her within one standard deviation (8.61) of the mean. The estimated height from the femur length (left length 41.5 cm) using Boldsen's method (1984) was 156 cm, with the average adult female from the Tirup cemetery being 161.91, placing her again within one standard deviation (5.94) of the mean.

In addition to the multiple developmental defects described in this paper, the woman had several other abnormalities worth noting. The first is the complete aplasia of the permanent upper lateral incisors. In their place, the deciduous canines have been retained. There are also many severe dental caries extending into the pulp chamber or with complete destruction of the crown, and these are more numerous than usually seen in an individual of this age from Tirup. Enamel hypoplasias are present on many teeth, indicating stress between 3 and 6 years of age (method from Goodman and Rose, 1990), although these enamel defects are not uncommon in this population (Boldsen, 1997a). Furthermore, the woman suffered from an infectious or neoplastic disease that caused lytic lesions throughout the skeleton. These are visible in the skull, vertebrae, ribs, pelvis, and several long bones. It is hypothesized that the process producing these lesions caused or contributed to her early death. These additional abnormalities may have been indirectly related to the developmental defect, although there is no evidence on which to judge this.

The malformations of the vertebrae, ribs, and sternum of this woman most likely caused her to look unusual, but the skeleton shows no evidence that these caused extreme pain, trauma, or disability. There is no evidence for scoliosis. The muscle attachments on both sides of body are equal and unremarkable, both in the axial and appendicular skeleton. There is no evidence of arthritis from unequal or overuse of any of the joints, and no signs of atrophy from disuse. It has been shown in modern populations that transitional vertebral and other defects often do not cause back pain (van Tulder et al., 1997).

What is most amazing about this case is that we have her adult skeleton available to study at all. In a study of 940,092 live births registered in Spain between 1976 and 1991, only 110 were registered with major segmentation field defects of the vertebrae and ribs (excluding minor defects that are difficult to identify in living individuals like absence of a rib or a single hemivertebra), constituting 0.01% of the total population (Martinez-Frias and Urioste, 1994). Only two of those were sequence defects (Martinez-Frias and Urioste, 1994), of the type seen in the skeleton from Grave 82. Of children born with all types of blastogenetic field defects (including vertebral segmentation defects), 35.73% died at or soon after birth, even with modern neonatal care in hospitals (Martinez-Frias and Frias, 1997b). Most cases of vertebral segmentation anomalies are accompanied by soft tissue deformations, as would be expected by disrupting the basic process of segmentation so early in development (Loder and Dayioglu, 1990; Martinez-Frias and Urioste, 1994). Her survival to adult age was very unlikely.

TABLE 1. List of vertebrae from Grave 82, with developmental defects noted

Vertebra number	Malformation	Description
C1	Normal	
C2	Normal	
C3	Normal	
C4	Normal	
C5	Normal	
C6	Normal	
C7	Normal	
T1	Normal	
T2	Block	Left arch and left transverse process fused with T3
T3	Block	Left arch and left transverse process fused with T2
T4	Normal	
T5	Block	Left arch and left transverse process fused with T6
T6	Block	Left arch and left transverse process fused with T5
T7	Normal	
T8	Normal	
T9	Normal	
T10	Normal	
T11	Normal	
T12	Missing pedicle	Right pedicle missing
T12a	Border shift	Arch lumbarization
L1	Border shift	Arch thoracized, missing right transverse process
L2	Normal	
L3	Block	Body and inferior articular surfaces fused with l3a
L3a	Block	Body and superior articular surfaces fused with L3, body deformed, wedge-shaped on left side
L4	Normal	
L5	Normal	
S1	Border shift	Lumbarized, right arch not fused and missing alae
S2–S6	Normal	

Fig. 2. Photograph showing the entire presacral vertebral column (right lateral view).

Description of defects

The skeleton G82 has multiple developmental defects in the vertebrae, ribs, and sternum. These are described in detail below and summarized in Table 1.

Total number of vertebra. The number and pattern of the vertebrae are extremely unusual, with a total of 26 (Fig. 2). There are the typical seven cervical vertebrae (Fig. 3). There are, however, 13 complete thoracic vertebrae (Fig. 4) and six lumbar vertebrae (Fig. 5). In addition, there are six sacral vertebrae (malformed, see below) (Fig. 6), and the number of caudal units could not be ascertained due to preservation. A thorough search of the literature on vertebral anomalies and defects, both in medical and anthropology journals and reports, found no other cases with 26 total presacral vertebrae, especially in the case where there were the correct number or supernumerary sacral vertebrae. Barnes (1992) refers to the maximum human number as 25, as does Kaufman (1974) in a study of 462 complete vertebral columns.

Block vertebra. Three sets of vertebrae are congenitally fused. Thoracic vertebra T2 and T3[1] are fused unilaterally in the arch on the left side (Fig. 7), as are thoracic vertebra T5 and T6 (Fig. 8). In these blocks, the vertebrae share a transverse process on the left side, which has two articulations for the individual ribs. These defects are restricted to the arch only, as the bodies are clearly separate units. The midline is the exact

[1]Throughout this paper, the vertebra will be referred to by their number. Cervical vertebra are indicated with a "C," thoracic vertebra with "T," and lumbar with "L." The additional vertebra not found in the normal human skeleton are indicated by an "a" after the number of the closest cranial vertebra (see Table 1).

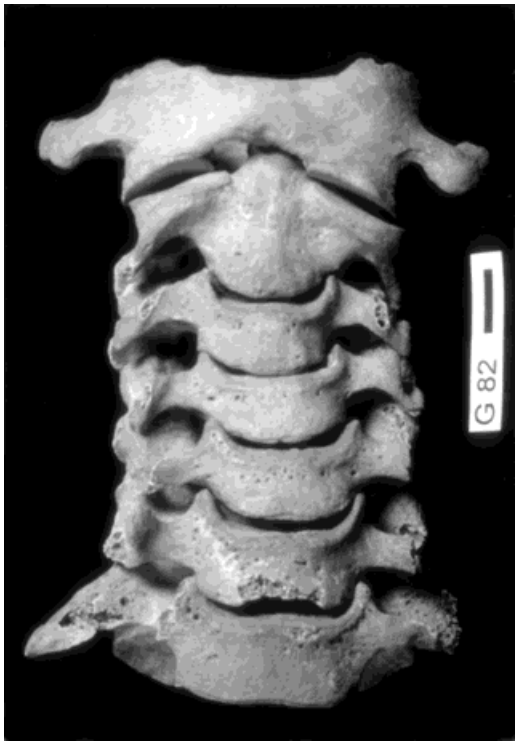

Fig. 3. Photograph showing the cervical portion of the vertebrae (anterior view).

Fig. 4. Photograph showing the thoracic portion of the vertebral column (anterior view).

division between the areas of fusion and separation in the arch.

Lumbar vertebrae L3 and L3a are fused very differently (Fig. 9). On the right side, the bodies of the two vertebrae are completely fused, with little to indicate the division between the two elements. On the left side, L3a is a separate vertebral element, although the fusion of the bodies and arches keep it attached to the anterior element. The arches are separate, unlike the fused thoracic blocks.

Border shifts. There are several border shifts and transitional vertebrae found in this individual. The occipitocervical and cervicothoracic borders appear to be normal. However, there is some shifting at the thoracolumbar border (Fig. 10). T12a has rib facets (and at least one rib), designating it as a thoracic vertebra. However, the arch and transverse processes have some lumbar features. The arch of L1, however, does not have fully developed lumbar features, with some thoracization, more evident on the left side. Therefore, we designate them both as transitional, without a clear cranial or caudal shift.

The first sacral vertebra has a clear caudal shift on the right side (Fig. 6). The left ala is shaped as a normal sacral element. The right arch is completely formed as a lumbar, and the right auricular facet with the ilium is shifted down to start on S2. The body of the vertebra is shaped as a sacral, with a smaller inferior than superior surface.

The sixth sacral may be the result of a caudal shift of the first caudal vertebra, but without the caudal vertebra for comparison, it is impossible to tell if this is a shift or a true extra element.

Missing pedicle. The twelfth thoracic vertebra (T12) is congenitally missing the pedicle on the right side (Fig. 11). The arches are correctly formed and meet at the midline, and the superior and inferior articula-

Fig. 5. Photograph showing the lumbar portion of the vertebral column (right lateral view).

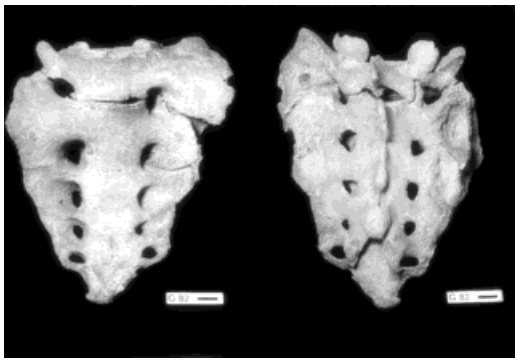

Fig. 6. Photograph showing sacrum, with partial lumbarization of S1 (on left, anterior view; on right, posterior view).

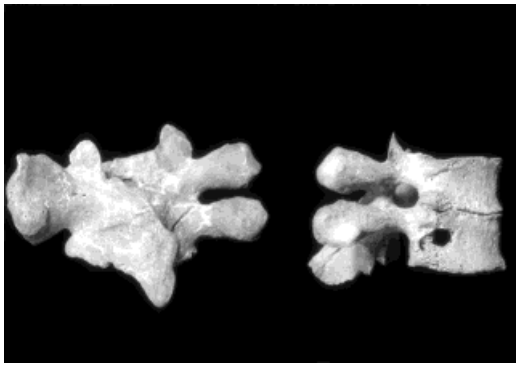

Fig. 7. Photograph showing the thoracic vertebrae T2 and T3 (on left, posterior view; on right, right lateral view).

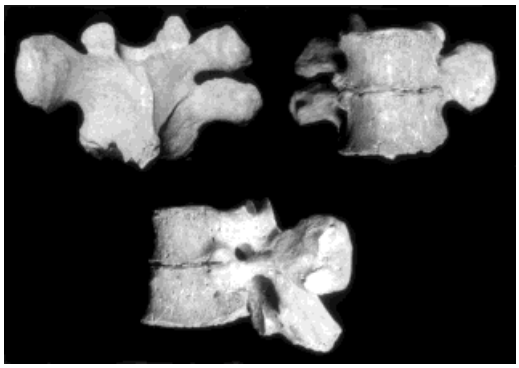

Fig. 8. Photograph showing the thoracic vertebrae T5 and T6 (on left, posterior view; lower center, left lateral view; on right, anterior view).

tions are formed correctly. Barnes (1992: 124) states that "Aplasia of the pedicles is rare. . .; it is usually in the cervical spine between the fourth and seventh cervical vertebrae. Missing lumbar pedicles are even rarer than cervical cases, and *they are unheard of in the thoracic spine*" (emphasis ours). In G82, it is clear that this is indeed a case of aplasia of the pedicle in the thoracic spine, and not caused by traumatic injury or a disease process.

Rib number. This individual had 13 ribs on each side, compared to the normal 12 pairs. On the right side, ribs 2 through 12a have been preserved. The thirteenth rib appears as a normal twelfth, with normal length and no articulation on the sternal end. On the left side, ribs 1 through 12 are preserved. Unfortunately rib 12a is not present. Its existence is marked by the rib facet on the body of T12a.

Malformed sternum. The sternum of this individual is malformed, with articulations for the costal cartilage of the normal

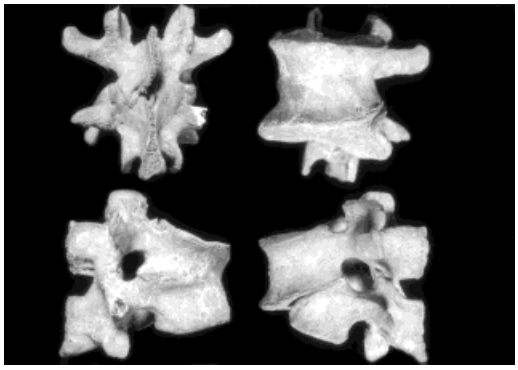

Fig. 9. Photograph showing the lumbar vertebrae L3 and L3a (upper left, posterior view; upper right, anterior view; lower left, right lateral view; lower right, left lateral view).

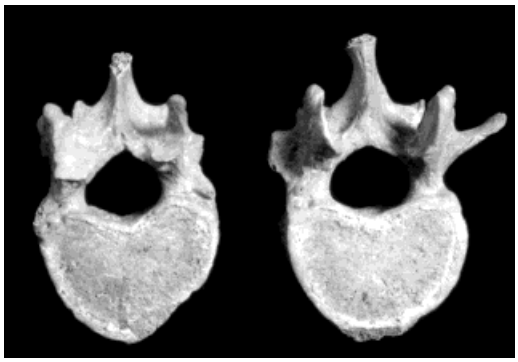

Fig. 10. Photograph showing thoracic vertebra T12a (on left) and lumbar vertebra L1 (inferior views).

seven ribs on the right side and only six on the left (Fig. 12). The manubrium has a normal appearance.

Grave 82 and the Tirup population

In Tirup cemetery, there were 14 individuals with single or multiple vertebral abnormalities (Table 2), out of 155 adults with at least 25% of the vertebral column preserved well enough to be studied. As problems in development may not be recognized in younger children with immature vertebral elements, individuals with vertebrae in the pre-fusion state were not included. The identified vertebral abnormalities, other than in Grave 82, were relatively minor. Border shifting, complete and incomplete sacral spina bifida, congenitally fused vertebrae, and extra vertebra were found.

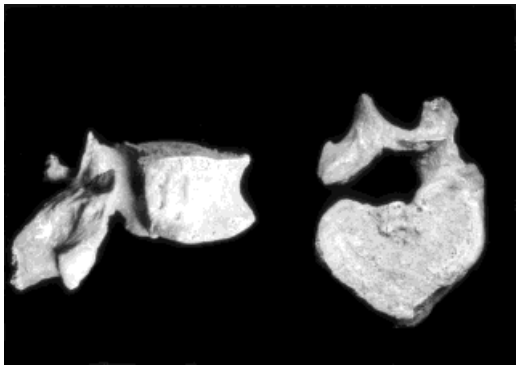

Fig. 11. Photograph showing thoracic vertebra T12, with missing pedicle (on left, right lateral view; on right, superior view).

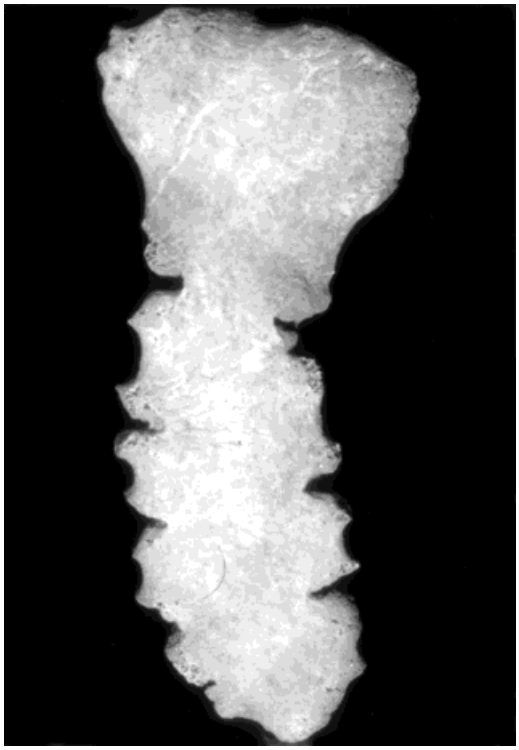

Fig. 12. Photograph showing the sternum (anterior view).

These location of the affected individuals within the Tirup cemetery was plotted, and tests were done to determine if there was any spatial patterning of individuals. There was no visible clustering, and, using a k-function analysis in the statistical program

TABLE 2. Vertebral abnormalities found in Tirup cemetery

Vertebral abnormality	Location	Number of individuals afflicted
Border shifting	Occipitocervical	2
	Thoracolumbar	2
	Lumbosacral	3
Fused vertebrae	Thoracic	2
Extra vertebrae	Thoracic	1
	Lumbar	3
	Sacral	2
Spina bifida	Sacral, incomplete	2
	Sacral, complete	2

S-Plus, it was determined that the placement did not deviate from a random pattern (J.D. Weets, personal communication). This would indicate that either these individuals with vertebral abnormalities were not closely genetically related, or that if they were close relatives, families were not buried together in the cemetery. The latter could be true, as during the earliest period the cemetery was in use, males were usually buried north of the church, and females south of it. During later use of the churchyard, this rule was not observed (Kieffer-Olsen, 1993; Kieffer-Olsen et al., 1997). The skeleton from Grave 82 is not usually close to other remains with vertebral defects, although she was buried during the later use of the cemetery.

DISCUSSION

Sequence and development of defects

Opitz (1993) specifically names vertebral segmentation defects as blastogenetic developmental field defects. Additionally, the pattern of defects seen in this skeleton may be called a *sequential developmental field defect*. The original blastogenetic defect was a segmentation error, causing several extra prevertebral elements (somitomeres) to be formed. These extra vertebrae are hypothesized to have caused the developmental chain reaction that created the cascade of defects seen in the adult skeleton. This is explored in further detail below.

Total number of vertebra. The extra vertebrae are a direct result of the formation of the extra somitomeres that occurred in the second week post-conception. Instead of the usual 51, it is supposed that at least two extra somitomeres formed in the more inferior portion of the embryo. These extra elements continued through the normal developmental sequence afterward, becoming vertebra, and causing all the other malformations.

Block vertebra. As the somitomeres were lining up on the midline to form the somites, it appears that the extra number caused a delay in the arrival of some of the units. This later caused unequal separation of the loose and dense sections of the sclerotomes, and irregular formation of the vertebrae. This process is illustrated in the highlighted section of Figure 1. These malformations would have occurred during the third week post-conception.

The degree to which each set of vertebrae are fused depends on the exact timing of the fusion of the somites. With the blocks of T2 and T3, and T5 and T6, it appears that the timing was only slightly delayed. Because of this, the transverse processes on the right side are shared, and the majority of the fusion is in the right arches. In normal development, the sclerotome re-fuses and the dense tissue migrates posteriorly, to form the arches. It is the dense material that failed to separate correctly.

In L3 and L3a, the separation failure was much more severe, indicating that arrival of the somites at the midline corresponded even less. On the left side, the sclerotome was able to separate normally, forming a hemivertebra and separate arches. However, on the right side, the separation of the looser tissue never occurred, creating the two nearly complete, but fused bodies.

Border shifts. Border shifts occur at the thoracolumbar and lumbosacral borders. HOX genes, or other regulatory mechanisms, appear to account for these shifts. HOX proteins act linearly, and the combination of HOX genes activated at each vertebra determines its morphological identity (Collins, 1995). In this case, the two extra vertebrae seem to have diluted the linear accumulation of HOX products, "confusing" the identity of the transitional vertebra at the more inferior sections of the vertebral column. It does not appear to be a failure of the

HOX gene complex itself. This would have occurred during the third or fourth week post-conception.

Missing pedicle. The missing pedicle on T12 occurred during the chondrification stage of development. A missing chondrification site in the right arch would cause the gap, with the left site expanding beyond its normal midline point to create the other portion of the spinous process. However, the rib chondrification site was present, as indicated by the presence of the rib facet on the right side of the body. Because ossification only takes place in cartilage in the vertebra, bone was not created in the gap. This would have occurred during the sixth to seventh week post-conception. The developmental significance of this is not understood.

Rib number. This is a direct result of the extra number of thoracic vertebrae. The ribs arise from the dense sclerotome region that also forms the vertebral arch. After the 13 thoracic vertebrae were formed, the arches followed by producing ribs. This occurred in the sixth to seventh week post-conception.

Malformed sternum. It is clear that the malformed sternum is a direct result of the failure of segmentation of the thoracic vertebra, and the associated malformation of the ribs from those vertebrae. The ribs would have been unequal in timing due to the malformation of the upper thoracic vertebrae. Instead of growing evenly toward the sternum, inducing normal development, the sternum was met unevenly, causing the deformation seen. This occurred in the ninth week post-conception.

Genetic and environmental influences

In the case of the woman from Tirup, it is impossible to determine the cause of the defect. While we can be fairly certain that she (or her mother) was not exposed to many of the chemicals encountered in modern times, both environmental and genetic causes are equally likely. The presence of other individuals with defects in the cemetery, although minor, indicates that the population was susceptible. This may indicate a genetic predisposition, in a population that was very likely closely related. The spatial analysis of the Tirup cemetery shows no clear evidence for genetic relationships between affected individuals, however. Alternatively, there may have been environmental cause. Many disruptive agents were likely present in a 14th century village (e.g., alcohol, lead). The levels of morbidity and mortality were very high in the Tirup population, with most women who lived to adulthood dying during their reproductive years (B. M. Usher, unpublished data; Boldsen, 1997b). Fetal effects from maternal infection are a possibility. Finally, evidence from medieval sources shows that the quantity and variety of food available to peasants fluctuated seasonally, and was barely adequate during most of the year. Schulenberg and Kluger (1997), using evidence from 13th and 14th century English manor accounts, demonstrated that on average that a family of five in a farming village in Northern Europe did not produce the provisions that are generally considered to be the minimum yearly requirements of calories and nutrients. The diet of mothers may not have been completely sufficient to fulfill all the nutritional requirements of a developing fetus.

CONCLUSION

This paper has been a review of the literature on developmental defects and a case study, concentrating on the unique vertebral anomalies found in one Medieval Danish woman. It was determined that this individual suffered from a sequential developmental field defect of vertebral segmentation and development. The technique of looking for the developmental basis for these defects can be broadly applied. By determining the sequence and morphological cause of defects, individuals with different anomalies can be compared, and patterns of timing and results of defects can be seen that are rarely able to be seen in modern medical cases.

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